Pharmacogenetics of therapy for acute lymphoblastic leukemia (ALL)

Mary V. Relling, Pharm.D.

1986

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

1992

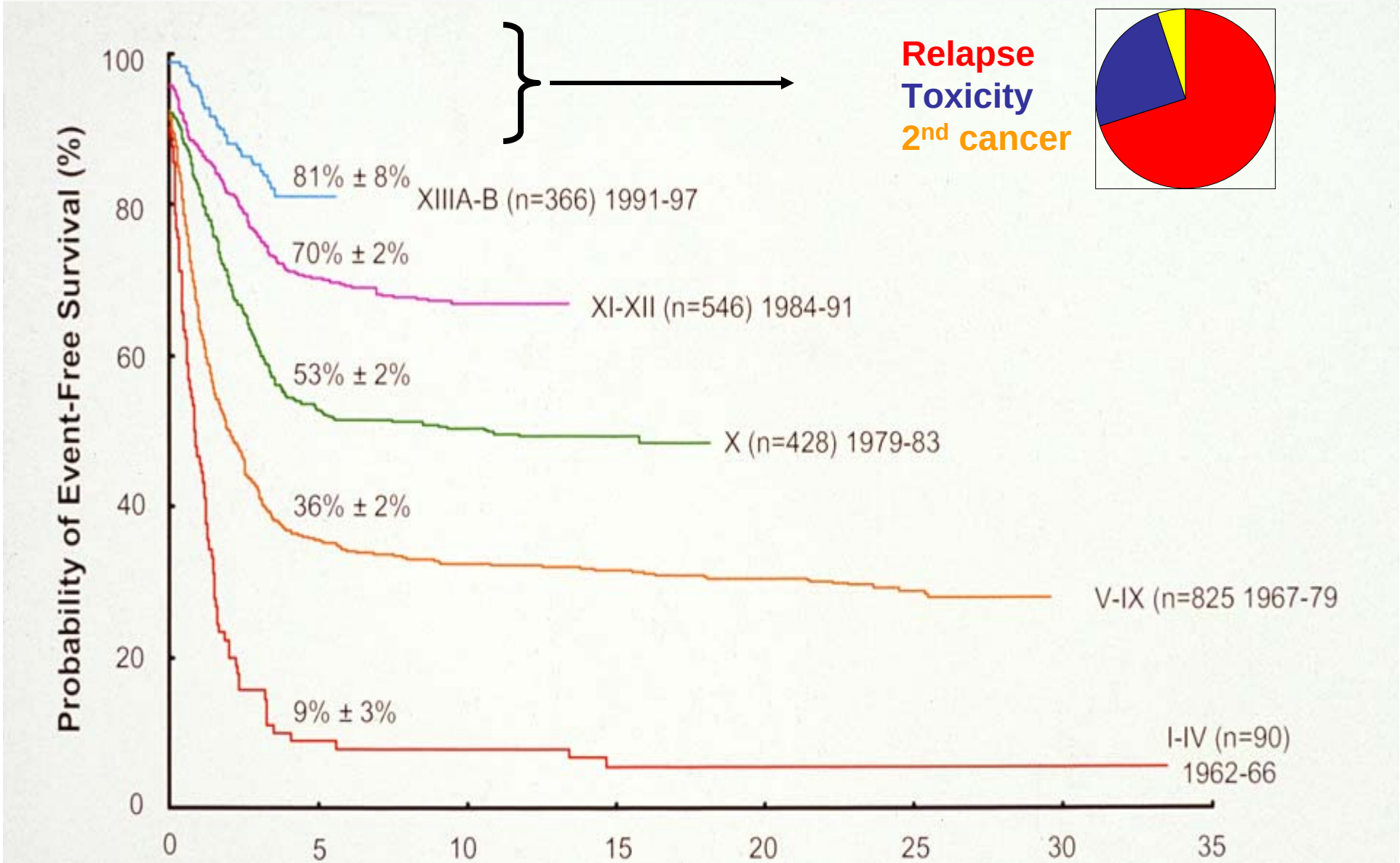
Children's Oncology Group

2000

PGRN

Pharmacogenetics Research Network

To what extent does pharmacogenetic variability contribute to failures in ALL?



At St. Jude, all pts with ALL are treated on front-line trials, and we have DNA going back to 1986….

History of Pharmacogenetics Trials at SJCRH

- Started with “stand alone” PGEN studies in 1986
- Incorporated into front-line ALL trials from 1994-to present
- Institutional tissue banking since 1989
- Opened “all comers” PGEN study in 1998

St. Jude Trial Pgenetic Objectives

- Pgen5 Protocol:
  - “To investigate whether genetic polymorphisms in genes encoding proteins involved in the metabolism or effects of drugs or environmental agents influence the disposition or effects of these xenobiotic substrates.”
- Treatment protocol (Total XVI):
  - “To identify pharmacogenetic, pharmacokinetic and pharmacodynamic predictors for treatment-related outcomes in the context of the systemic therapy used in the protocol.”

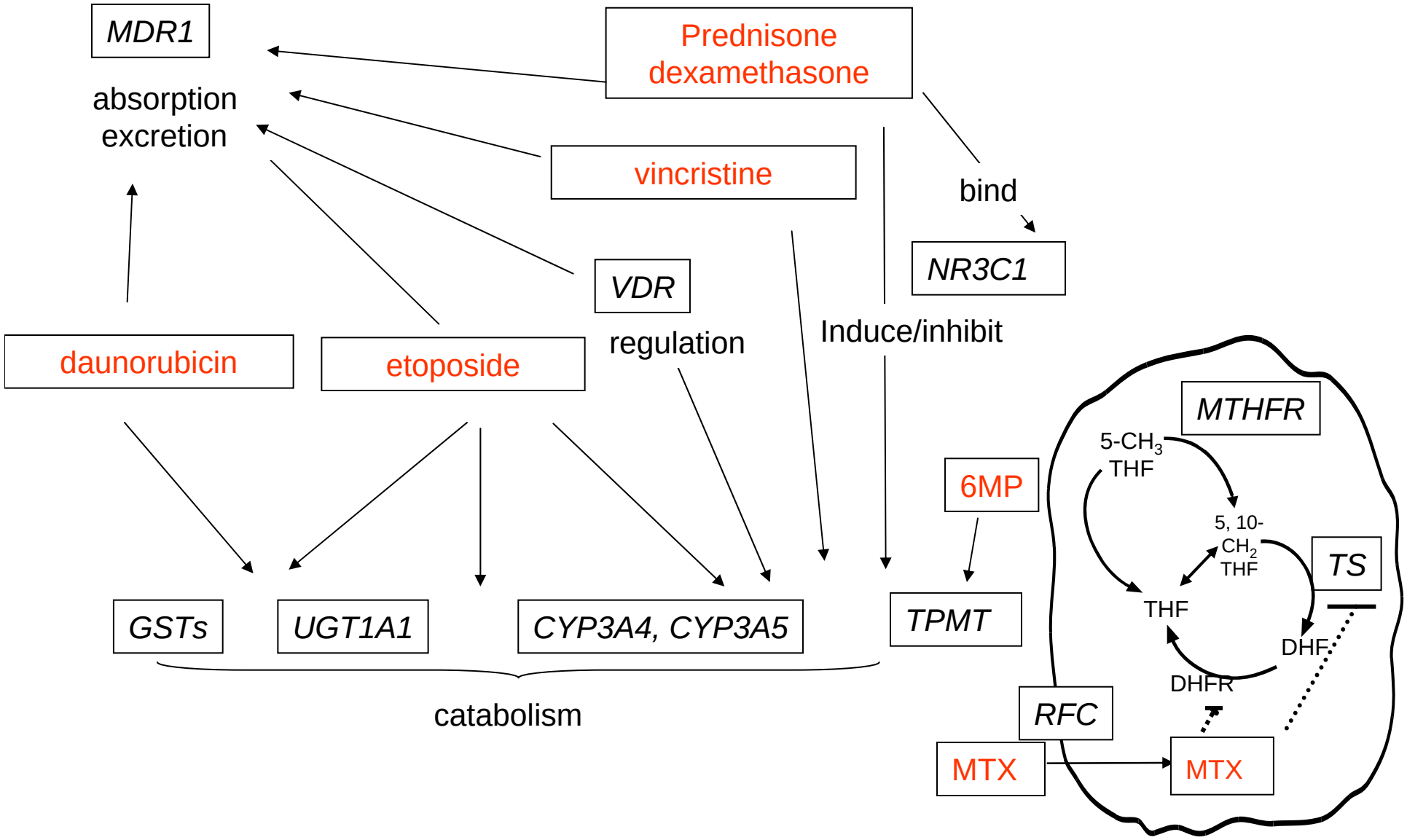
Pharmacogenetic Studies in ALL

- **Target Gene approach**
  - Assess ***known polymorphisms*** (e.g. VDR, P-gp, TPMT, GSTs, NQO1) vs outcomes (e.g. EFS, 2nd AML, AVN, etc)

Genome-wide approach

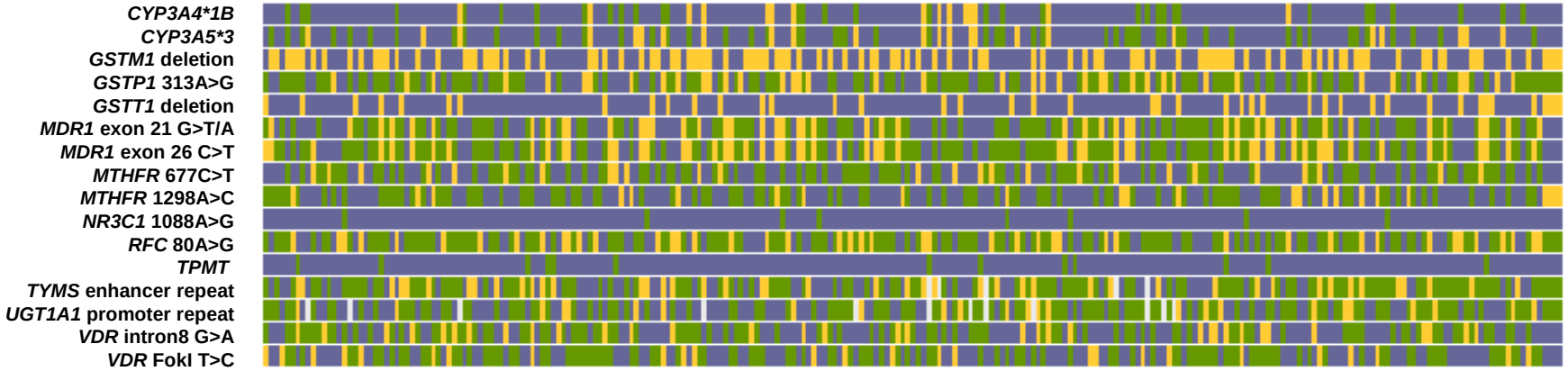
discover new targets (e.g. expression array, proteomics, genome wide scans)

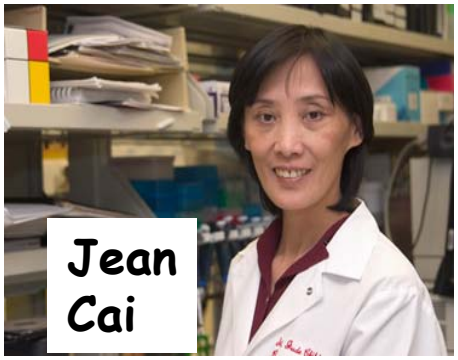
PGRN



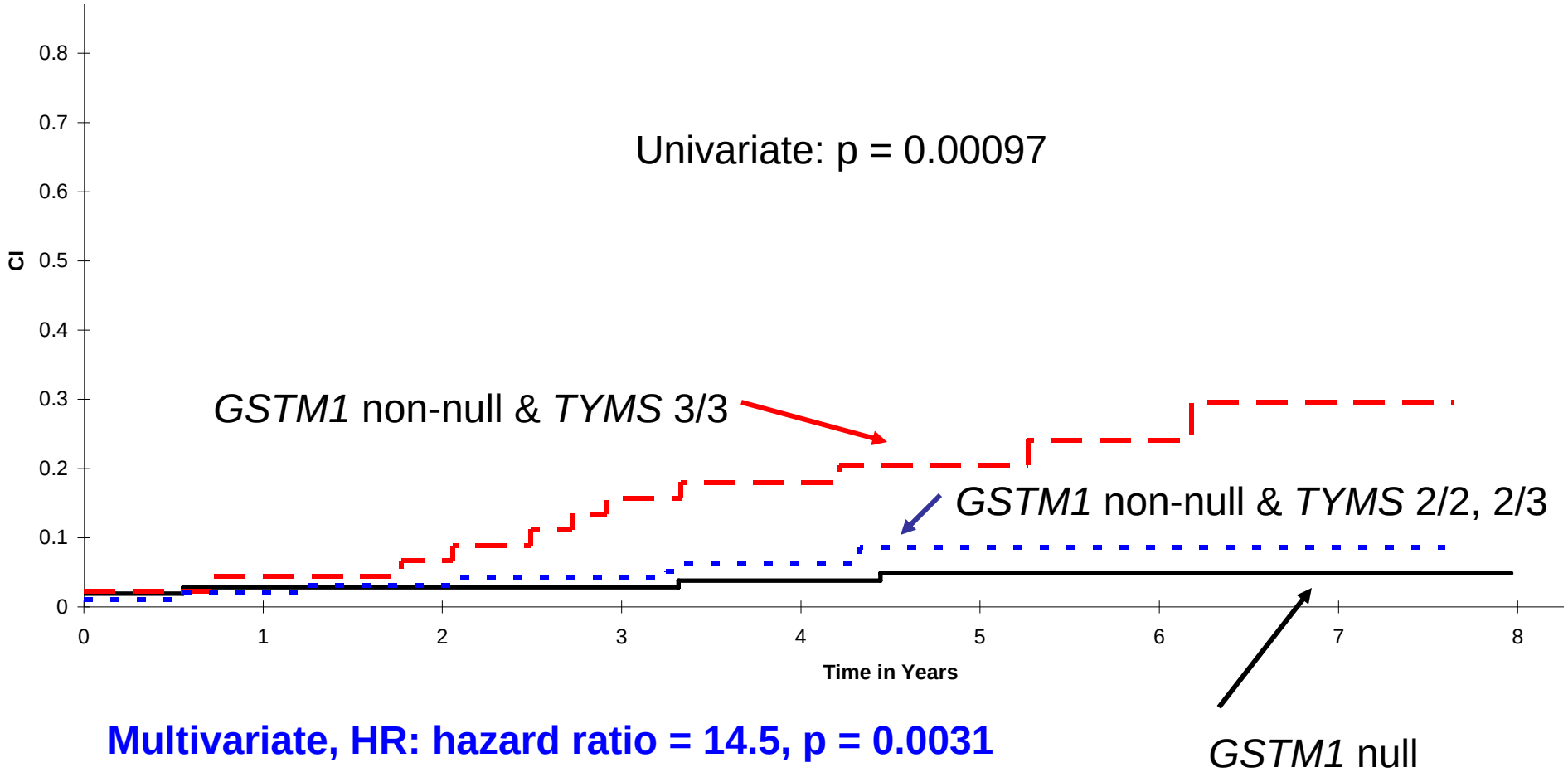
16 polymorphisms in 13 genes

Visual genotype for 246 pts on Total XIIIB study at 16 polymorphic loci





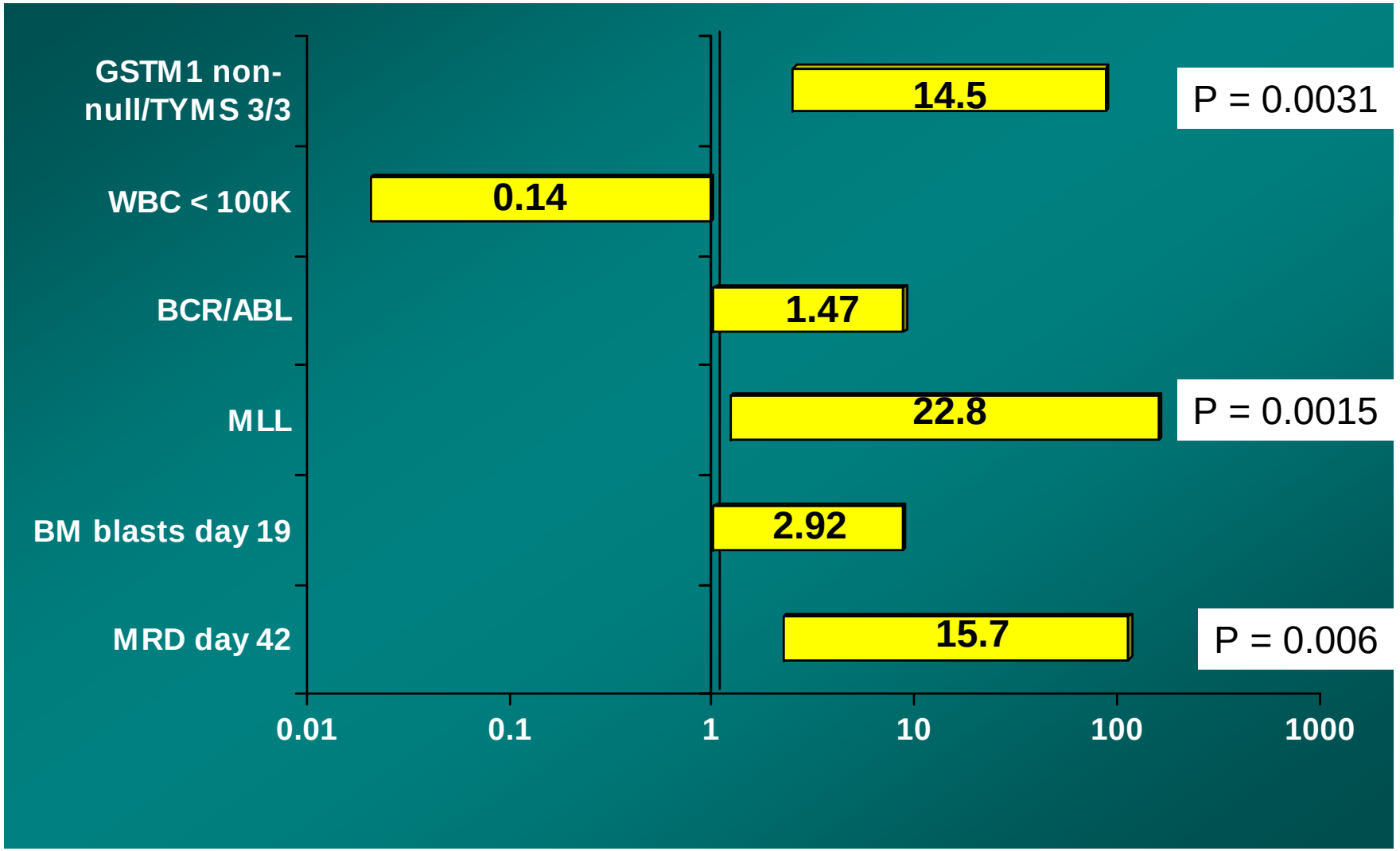
Combination of 2 genotypes, *GSTM1* and *TYMS,* Affected overall risk of hematologic relapse (n = 246)



Multivariate, HR: hazard ratio = 14.5, p = 0.0031

Blood 2005;105:4752-4758

Hazard Ratios associated with Germline Genotypes were on Par with "traditional" Prognostic factors in multivariate analyses



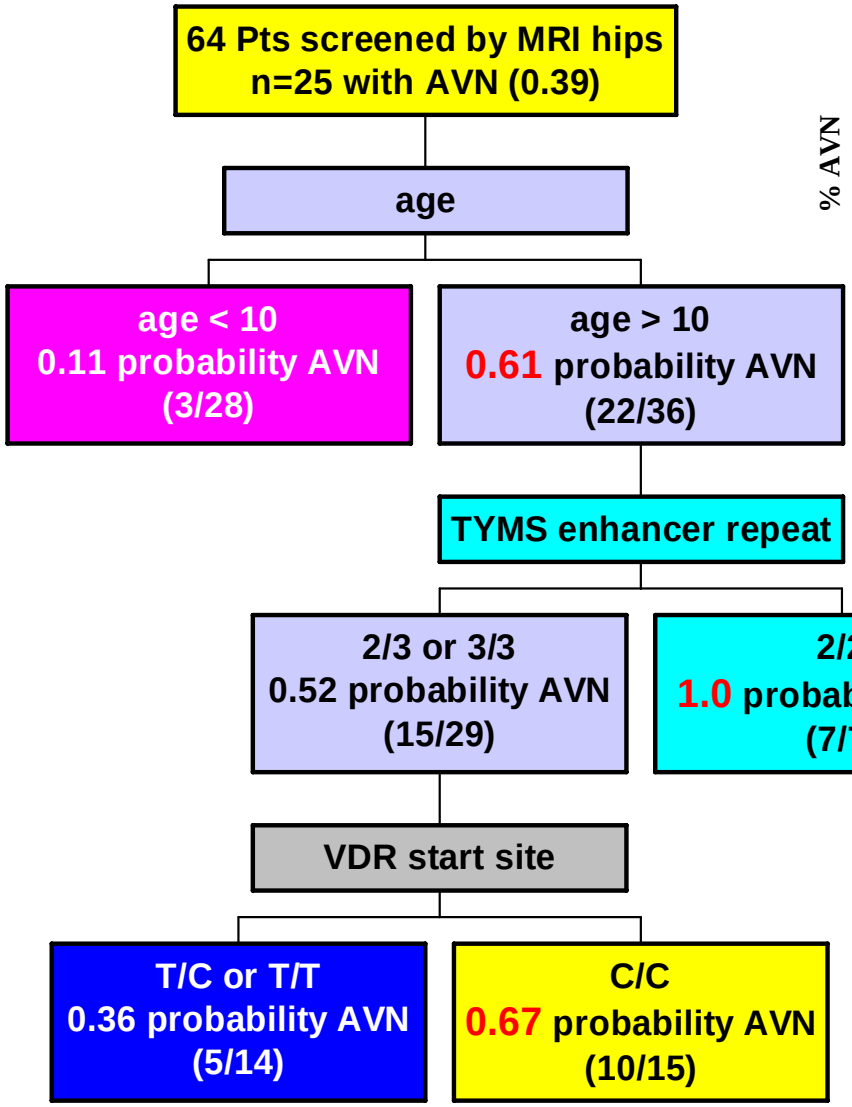
***Blood* 2005;105:4752-4758**

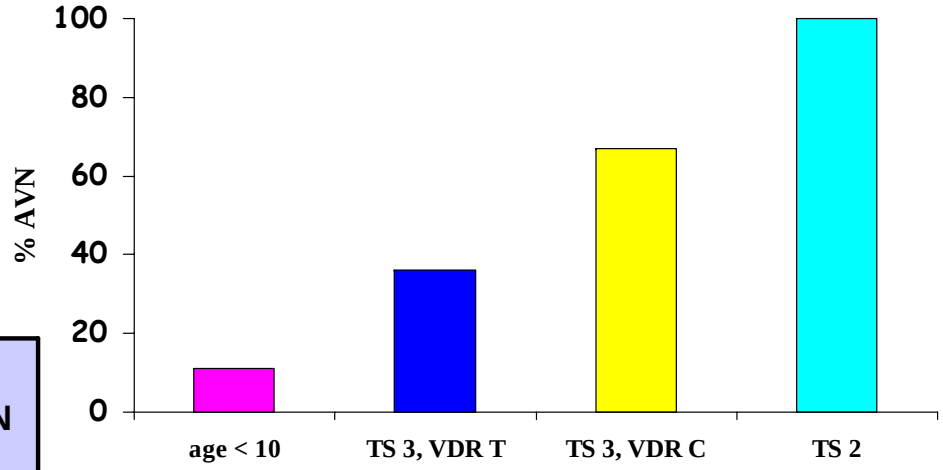
Drug-Induced Adverse Effects in ALL

- ~ all drugs: infection
- VCR: motor/sensory neuropathy
- MTX: cerebellar/cortical neurotoxicity
- MTX + others: gastrointestinal toxicity
- 6MP, MTX, others: hyperbilirubinemia

- glucocorticoids: avascular necrosis

Older age, *TYMS* genotype, and *VDR* genotype predict AVN risk





OR: 13.3 (1.4-129)

OR: 3.72 (1.20-11.6)

J Clin Oncol. 2004 22(19):3930-6.

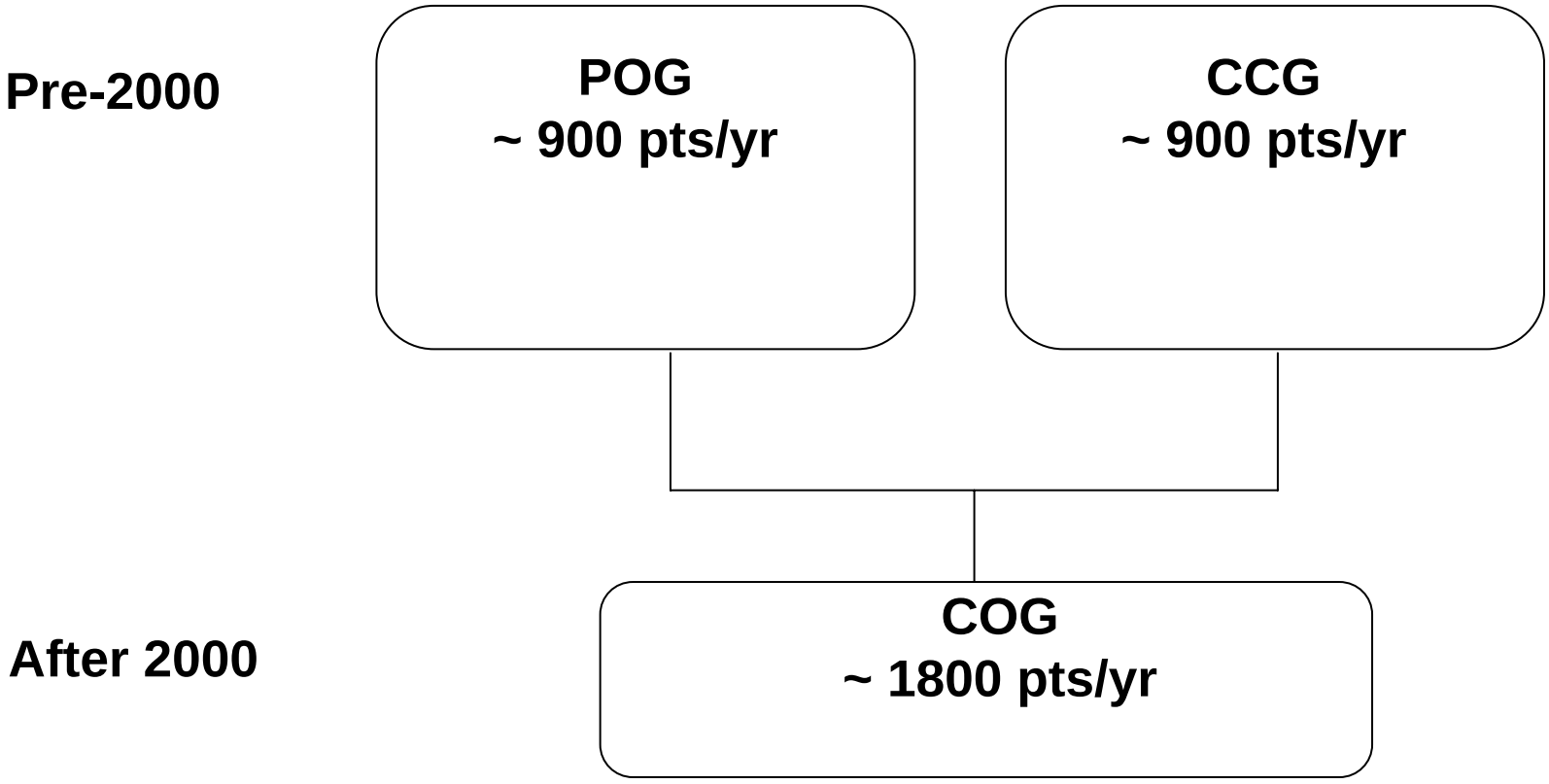
Summary: little overlap in outcome and toxicity genes

Relapse risk		Toxicity	
TYMS	3/3	*TYMS*	2/2 or 2/3
GSTM1	Non null	*CYP3A5*	GG
		UGT1A1	7/7
		VDR Fok 1	CC
		RFC	AA or AG

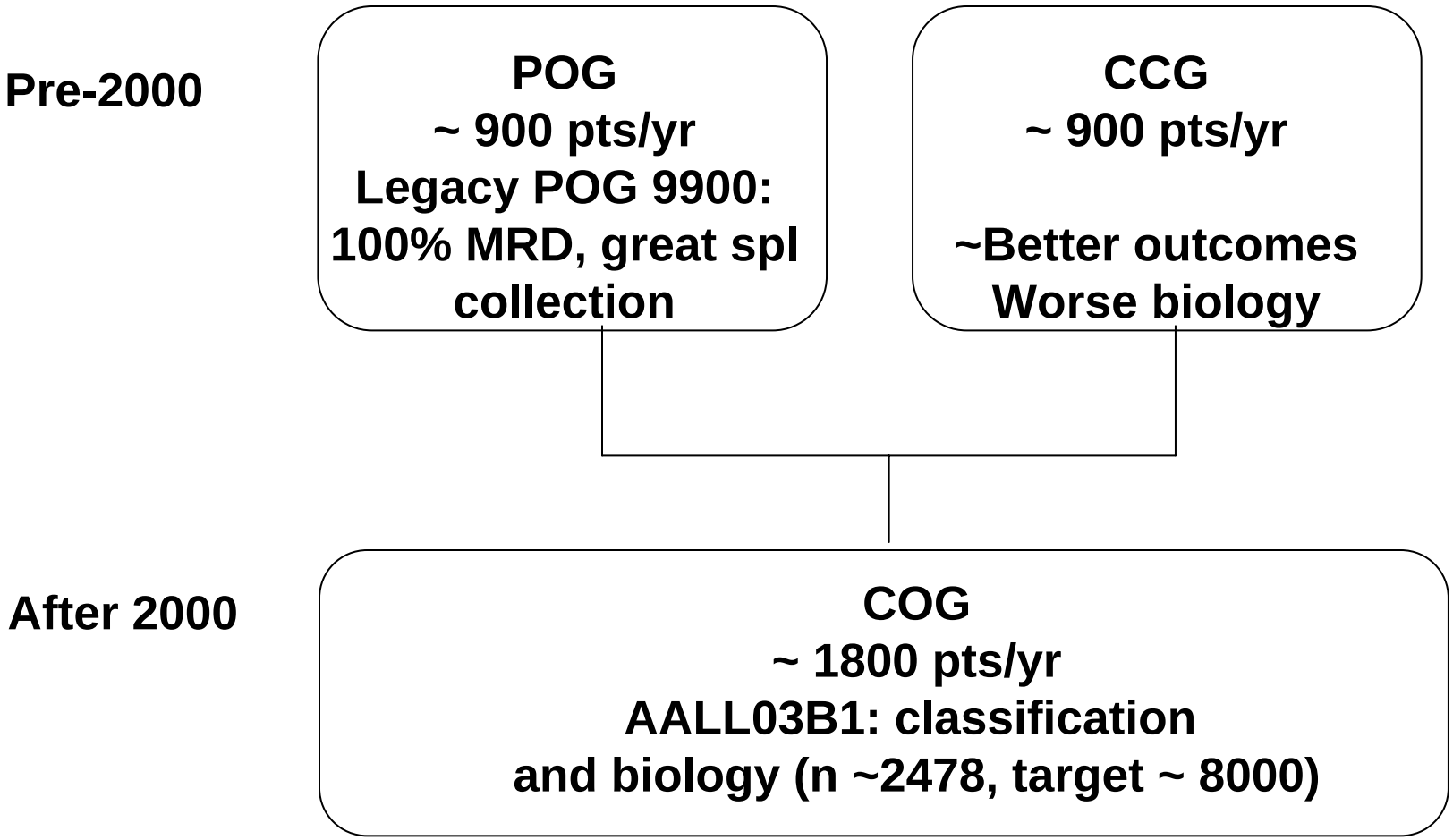
At St. Jude, we can move fast, but

- Need to replicate/fail to replicate
  - We need to see how penetrance of genotypic effects differs among tx protocols
- Need larger numbers
- Need to make a part of cooperative group trials (sex, age, disease status, genotype…)

NCI Cooperative Group studies in Childhood Cancer



NCI Cooperative Group studies in Childhood Cancer

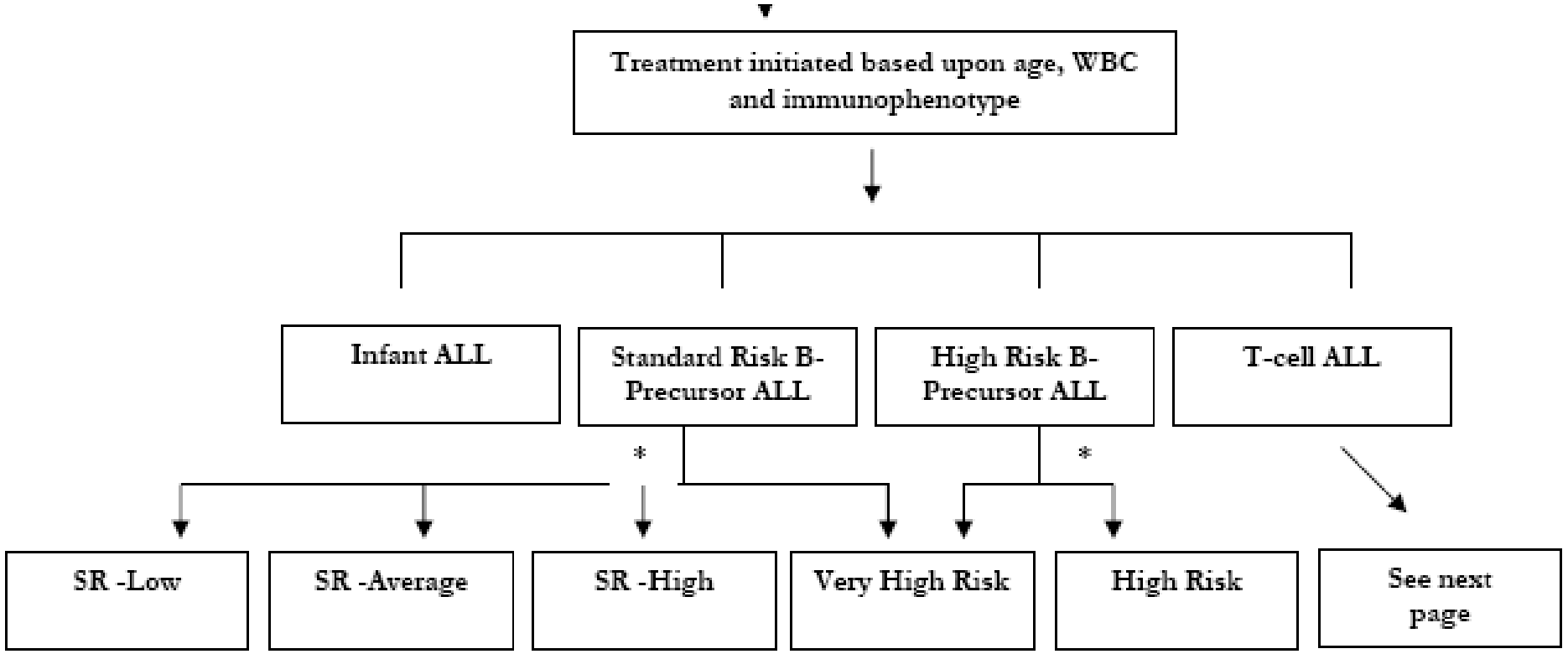


COG Pgenetic Objectives

- In classification protocol AALL03B1:
  - “To provide a mechanism for optional banking of leukemia and germline specimens for current and future research.”

AALL03B1

COG Model for classifying and treating ALL ~ 1800 pts/yr



* Day 29 Induction: Completion of Local and Reference Laboratory studies and refinement of initial risk group assignment

POG 9900: genotypes vs minimal residual disease (MRD) (blood day 8, BM day 28); n ~ 2000

Polymorphisms in:

- *ADBR2*
- *CCR5*
- *CONNEXIN*
- *GSTP1*
- *MBP*
- *MDR1* X 2
- *MTHFR* X 2
- *NQO1*
- *P22*
- *RFC*
- *TPMT*
- *TYMS*
- *VDR* X 2

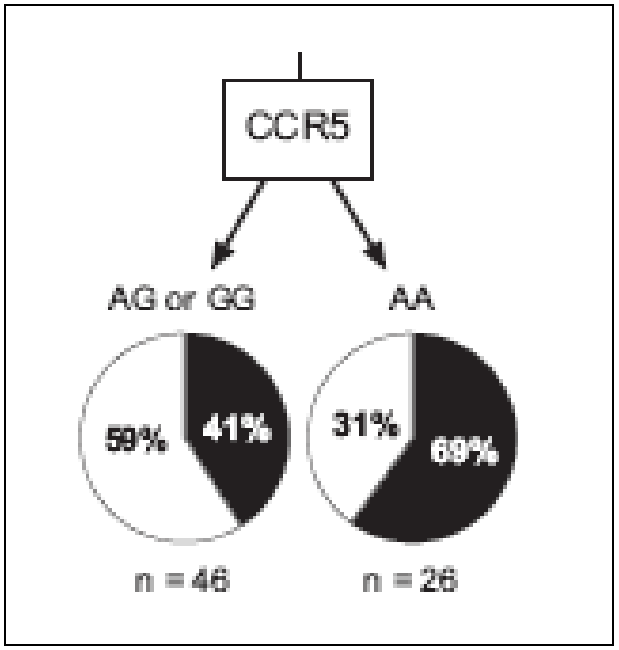
Confounding factors for MRD and for genotypes:

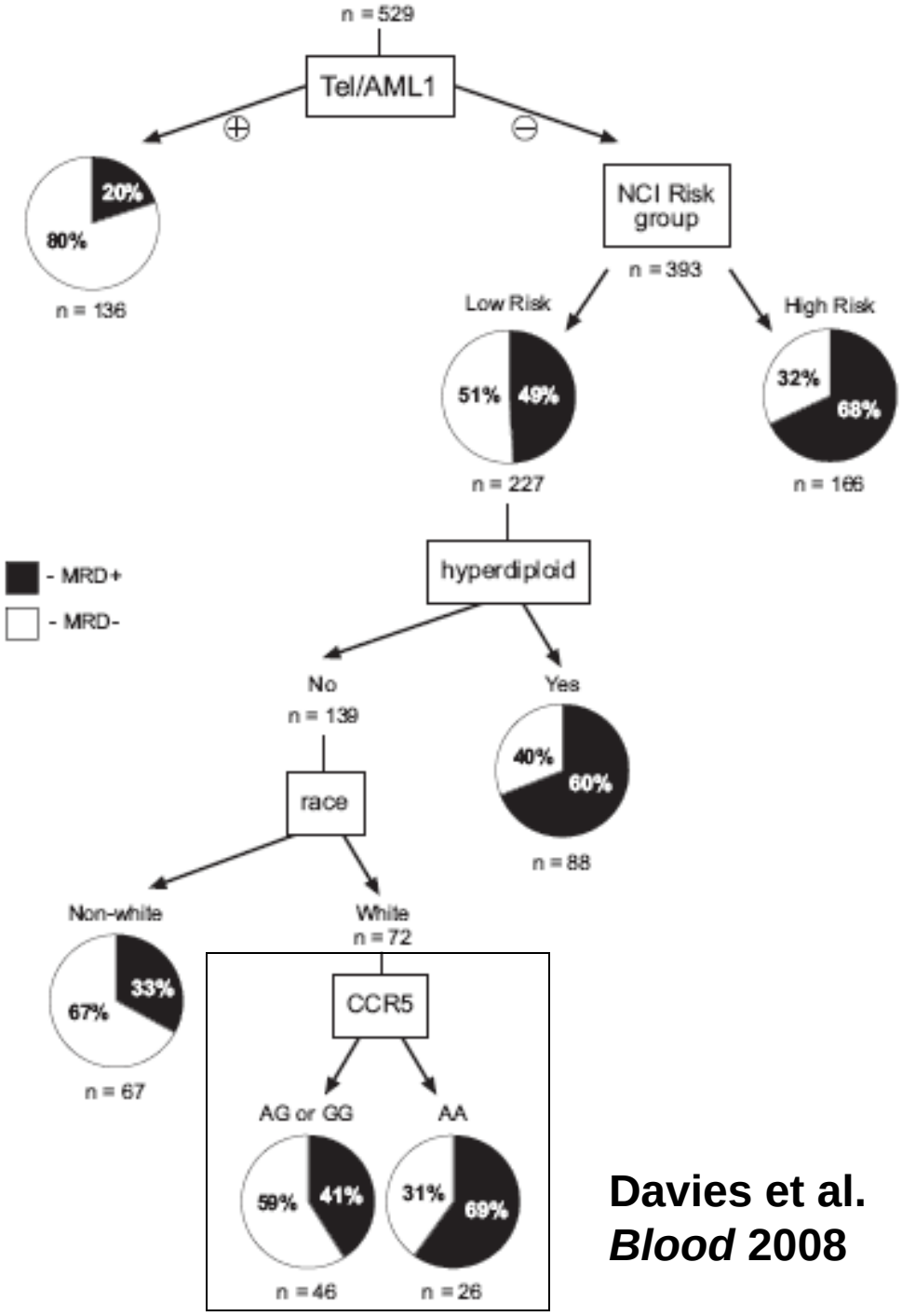
- NCI RISK
- RACE
- SEX
- IMMUNOPHENOTYPE
- TRISOMIES
- TRANSLOCATIONS: *TEL/AML1, BCR/ABL, MLL, E2A/PBX*
- PLOIDY (HYPO OR HYPER)

Davies et al.
***Blood* 2008**

Best vs worst:

MRD negative at day 8
Vs
MRD positive at day 29





Davies et al.
***Blood* 2008**

First major COG/PGRN collaboration

- PGRN investigator is also a COG investigator
- COG statisticians responsible for organizing clinical data, QC, descriptive stats.
- PGRN statistician responsible for genetic CART analysis

Pharmacogenetic Studies in ALL

- **Target Gene approach**
  - Assess ***known polymorphisms*** (e.g. VDR, P-gp, TPMT, GSTs, NQO1) vs outcomes (e.g. EFS, 2nd AML, AVN, etc)

Genome-wide approach

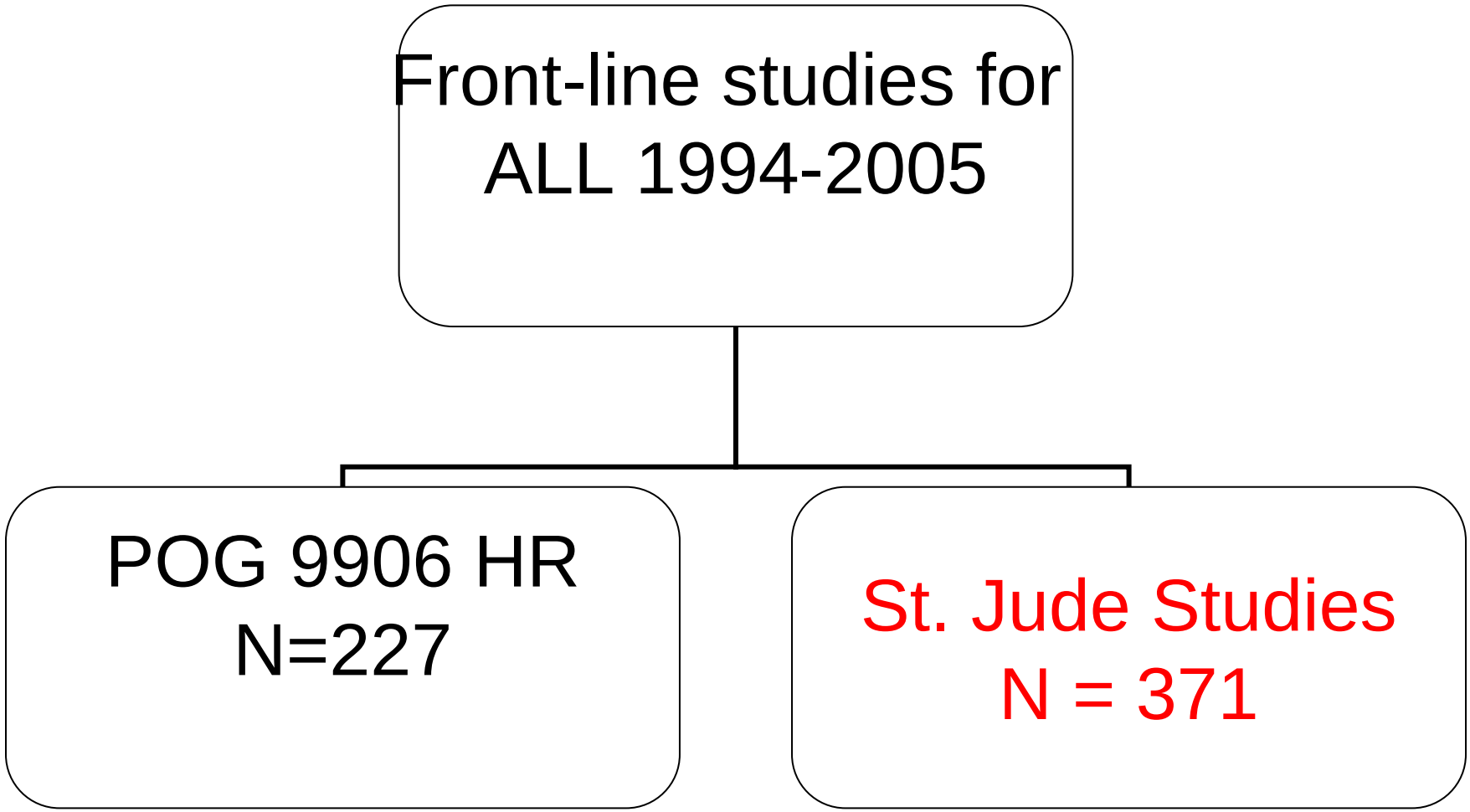
discover new targets (e.g. expression array, proteomics, genome wide scans)

PGRN

Genome-wide interrogation of germline genetic variations associated with treatment response in childhood acute lymphoblastic leukemia

Jun Yang1, Cheng Cheng1, Wenjian Yang1, Deqing Pei1, Xueyuan Cao1, Yiping Fan1, Stan Pounds1, Lisa Trevino1, Deborah French1, Dario Campana1, James Downing1, William Evans1, Ching-Hon Pui1, Meenakshi Devidas2, W.P. Bowman3, Bruce Camitta4, Cheryl Willman5, Stella Davies6, Michael Borowitz7, William L. Carroll8, Stephen Hunger2, Mary Relling1

Patients


Front-line studies for ALL 1994-2005
POG 9906 HR N=227
St. Jude Studies N = 371

Germline SNPs vs MRD

- 100K plus 500K Affy
- MRD by flow (Borowitz, Campana)
  - St. Jude: day 42
  - COG: day 28
- Assessed non-genetic factors predictive of MRD that differed in frequency between St. Jude and COG cohorts
  - Excluded ~ 10% of pts with these non-genetic characteristics from both groups

Agents	Dosages and Routes
Methotrexate*	2-4 dose IT ± systemic
Prednisone	40 mg/m^2, Daily, orally
Vincristine	1.5 mg/m^2, weekly, IV
Daunorubicin	25-30 mg/m^2, 2-3 doses, IV
Asparaginase	10,000 U/m^2, 6-9 doses, IM

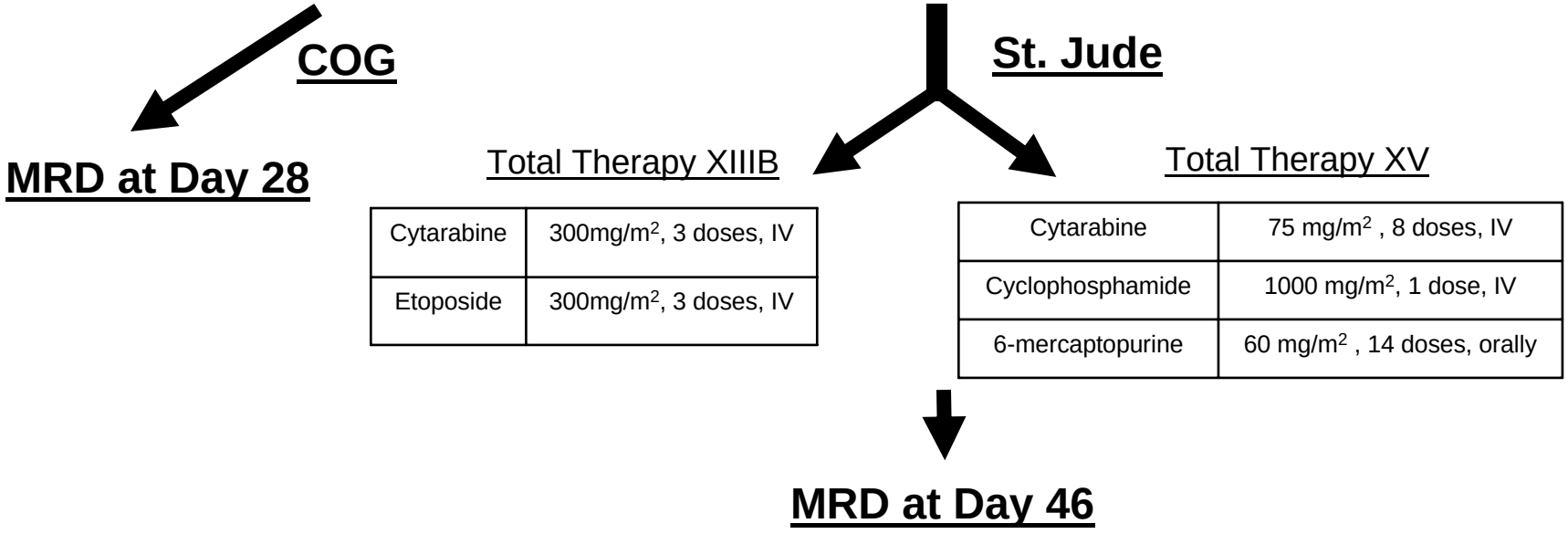


Figure 1S Remission induction regimens for St. Jude Total Therapy XIIIB, XV and COG 9906 protocols. IT: intrathecal; IV: intravenous; IM: intramuscular. *Methotrexate was given intrathecally, with or without cytarabine and hydrocortisone as prophylaxis for central nerve system disease in both St. Jude and COG. However, some St. Jude patients also received the drug orally or intravenously for a single day, in addition to the IT methotrexate. Further details of the treatment regimens can be found in references 21, 22 and at http://www.acor.org/ped-onc/diseases/ALLtrials/9906.html.

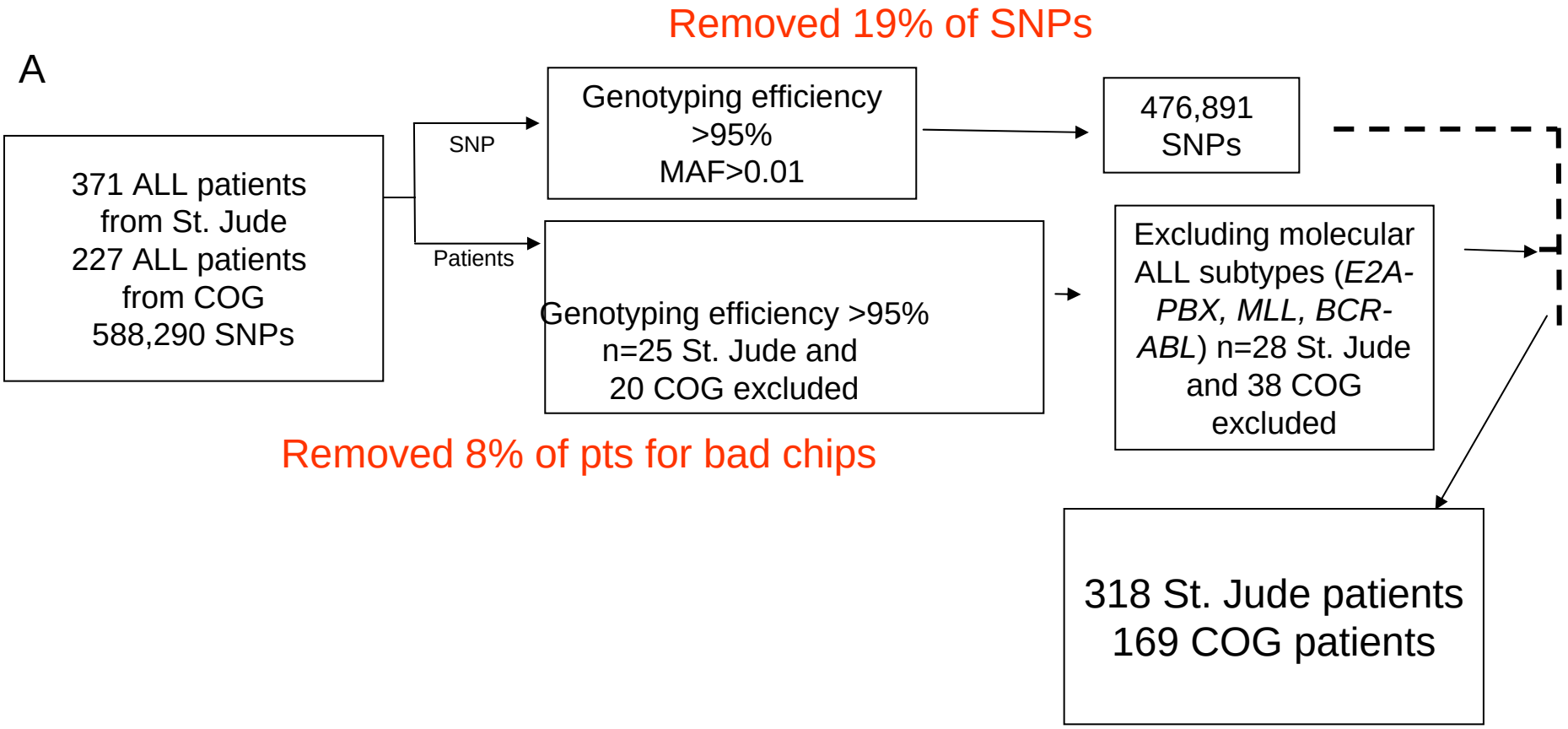
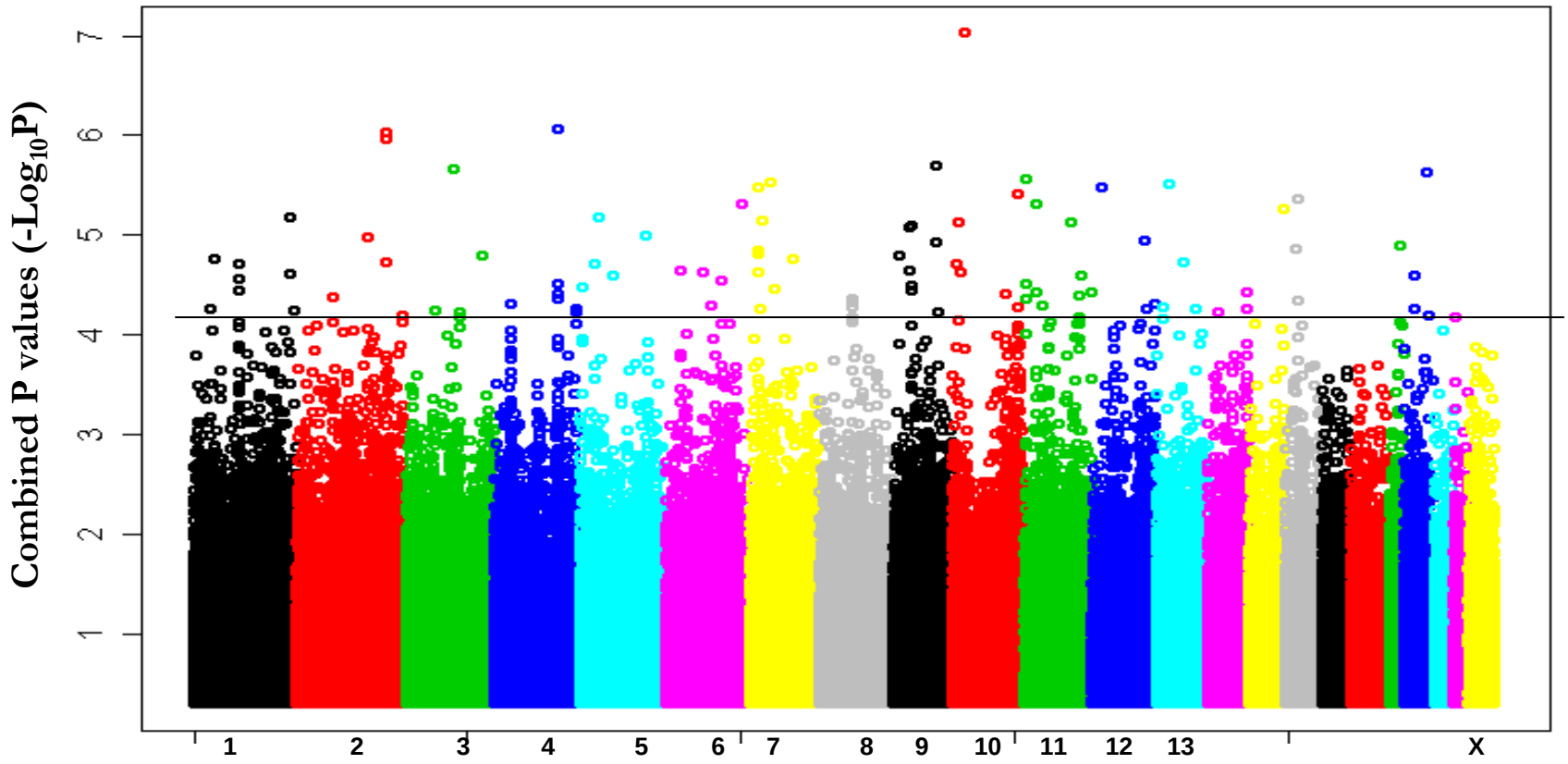
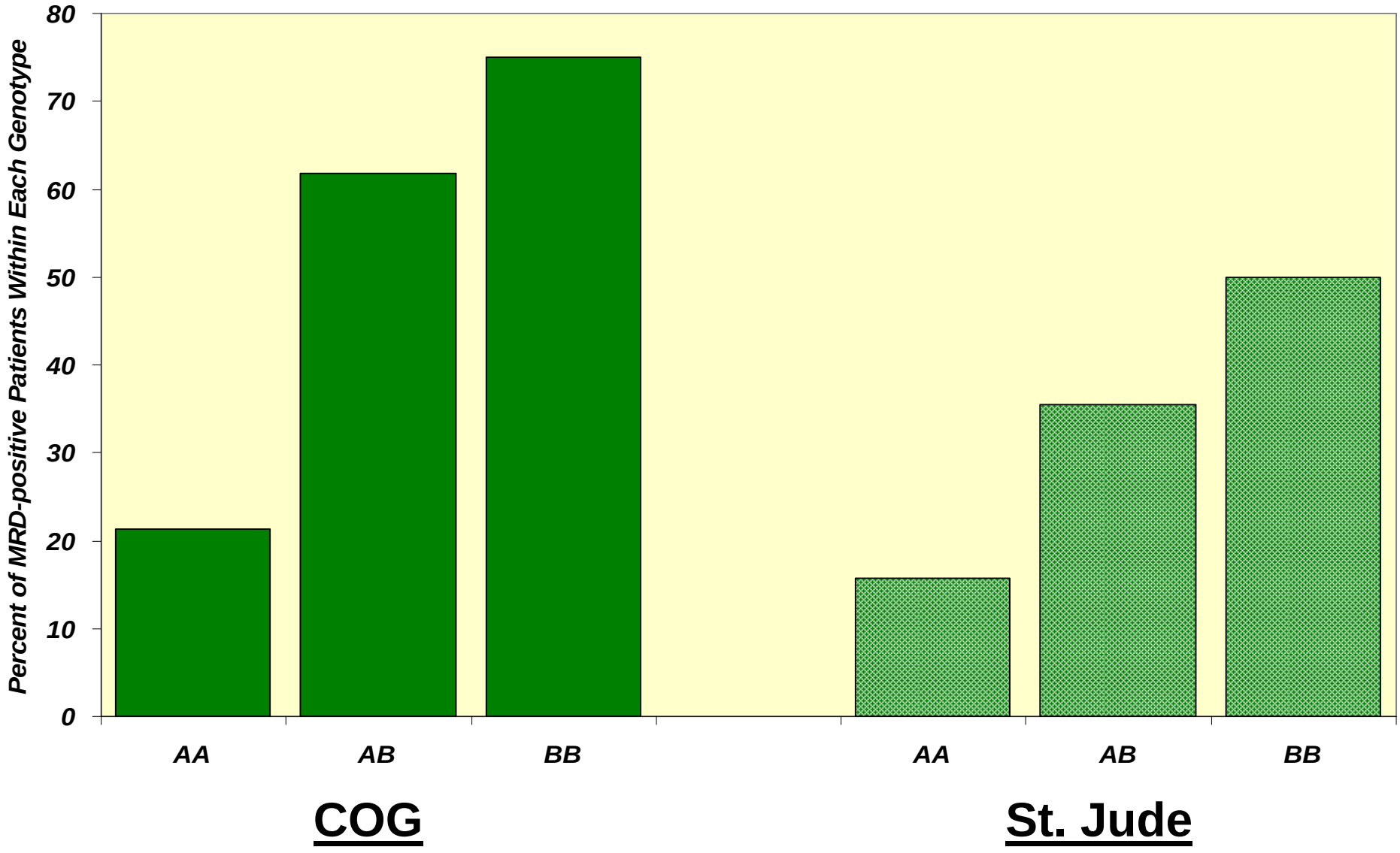


Figure 1. Schema of genotyping, quality control, and genome-wide association strategies. A, Outline of genotyping and quality control procedures. 476,891 SNPs, 318 patients from St. Jude and 169 patients from COG were included in the final analysis. MAF: minor allele frequency. **B, Outline of the genome-wide association analysis**. Genome-wide scan was performed in St. Jude and COG separately, using a permutation-based Spearman rank correlation. P value cutoffs were determined by false discovery rate (FDR) estimation and internal validation. Top ranked germline SNPs showing significant association ($P \leq 0.0125$) with MRD in the St. Jude or COG scan were cross-validated.

P values across the genome for association of SNP genotypes with MRD in both St. Jude and COG analysis (~ 102 SNPs overlap; only ~ 40% in genes).

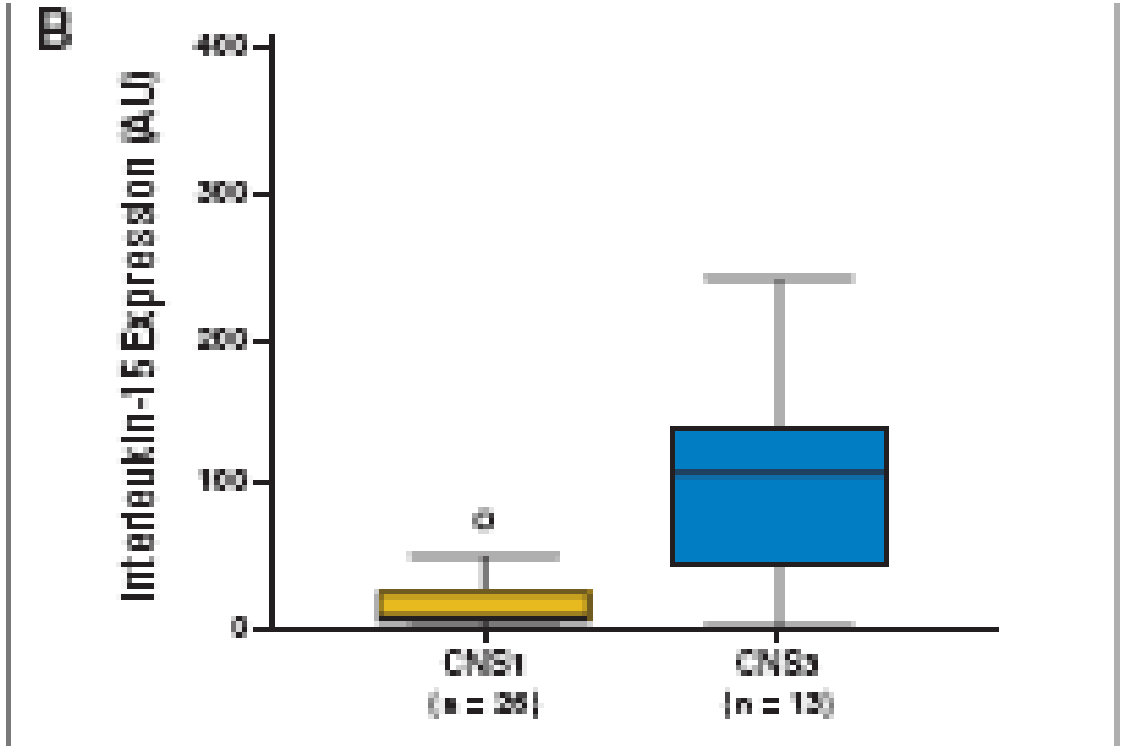


% of MRD positive pts was related to genotype at an overlapping SNP (IL15) in the 2 cohorts (COG and St. Jude)



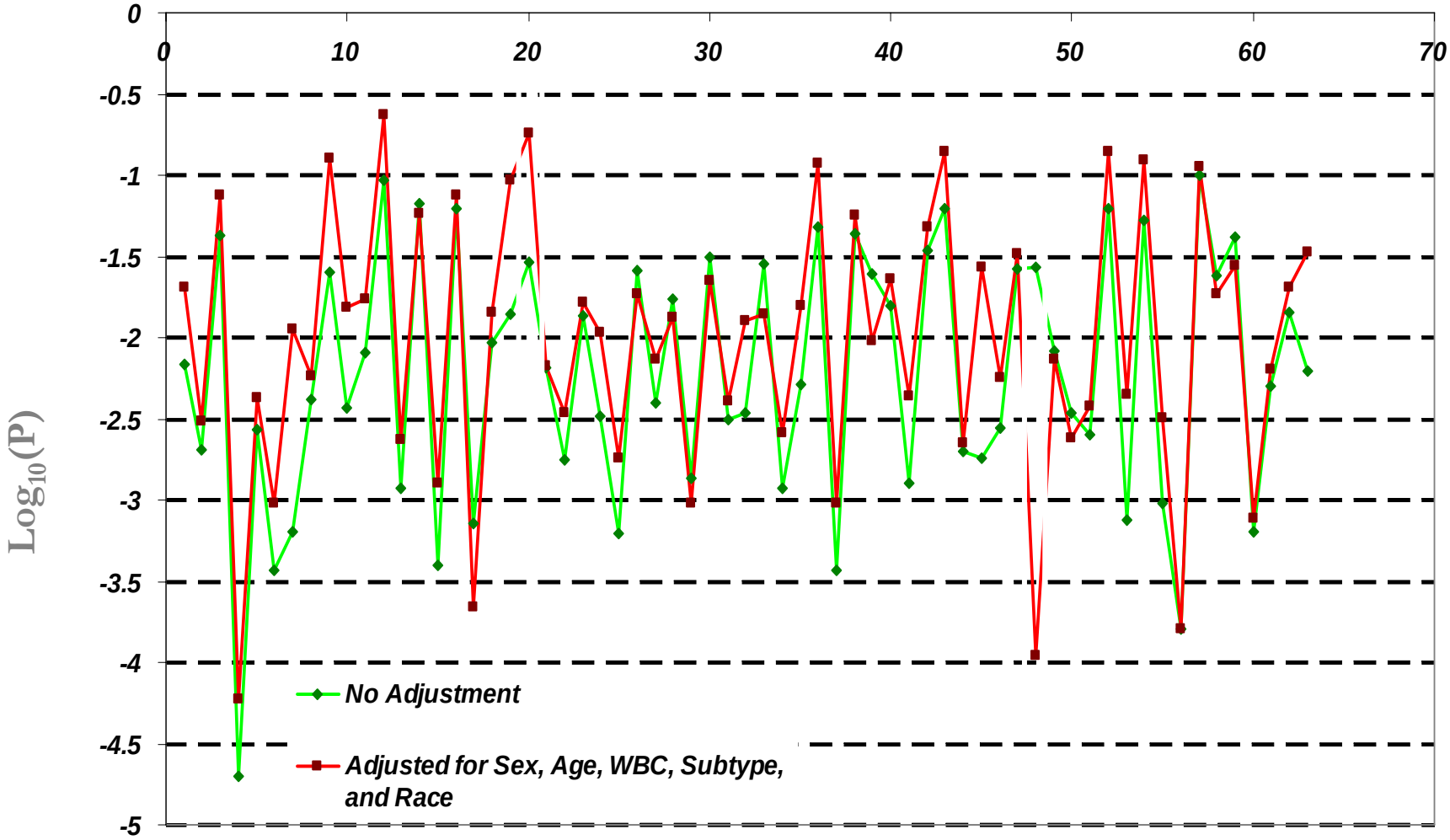
High Interleukin-15 Expression Characterizes Childhood Acute Lymphoblastic Leukemia With Involvement of the CNS

Gunnar Cario, Shai Izraeli, Anja Teichert, Peer Rhein, Julia Skokowa, Anja Möricke, Martin Zimmermann, Andre Schrauder, Leonid Karawajew, Wolf-Dieter Ludwig, Karl Welte, Holger J. Schlüsenera, Brigitte Schlegelberger, Martin Schrappe, and Martin Stanulla



J Clin Oncol 25:4813-4820. © 2007

P values for 102 overlapping SNPs remain significant after adjusting for “non-genetic” predictors of MRD



How to further prioritize among 102 overlapping SNPs?

- Examine function of genes (“pathway”)
- Compare with SNPs predicting response (PD) phenotypes in other data sets
- Compare with SNPs predicting exposure (PK) phenotypes in other data sets

Of 102 SNPs affecting MRD in both SJ and COG cohorts:

- 21/102 associated with anticancer drug pharmacokinetics (20 plausibly linked to MRD eradication---corresponding to greater drug exposure, less MRD)
  - 8/8 with MTX clearance
  - 5/6 with MTX accumulation in lymphoblasts
  - 7/10 with etoposide clearance)
- 23/102 predicted relapse
- 41/102 predicted very early response

Conclusions

- 102 germline genetic variants are associated with MRD in both SJ and COG cohorts
- High proportion associated with very early response, long-term relapse risk, and PK of antileukemic drugs
- Several plausible but “low on the pathway” candidates

PGEN studies in COG ALL

Study	n	Germ-line		comments
POG 9904/05	~2000	yes	ABTR02B1	*
POG 9906	250	yes	ABTR02B1; AALL06B1	*blast vs germline = TARGET *germline vs phenotypes (ongoing)
AALL03B1	Proj 8000	avail	Classification + indn	•Accrual ongoing
AALL0232	Proj 2300	avail	AALL06N1-neuro	HR B-lineage
AALL0434	1380	Avail	AALL06N1-neuro	T-cell
AALL0331	4600	Avail		•Std Risk
AALL03N1 ALTE03N1	720 800	Avail	Not primary	•Ethnicity •Late effects
AALL0433	Proj 418	avail	Not primary	•Int-HR relapse •VCR 1.5 vs 2.0

PGEN studies in COG ALL

Study	n	Germ-line		comments
POG 9904/05	~2000	yes	ABTR02B1	*germline genotypes using Affy 6.0—Dr. Reaman
POG 9906	250	yes	ABTR02B1; AALL06B1	*blast vs germline = TARGET *germline vs phenotypes (ongoing)
AALL03B1	Proj 8000	avail	Classification + indn	•Accrual ongoing
AALL0232	Proj 2300	avail	AALL06N1-neuro	HR B-lineage
AALL0434	1380	Avail	AALL06N1-neuro	T-cell
AALL0331	4600	Avail		•Std Risk
AALL03N1 ALTE03N1	720 800	Avail	Not primary	•Ethnicity •Late effects
AALL0433	Proj 418	avail	Not primary	•Int-HR relapse •VCR 1.5 vs 2.0

Interactions with PGRN

ALL Project:

- Weiss/PHAT Group (glucocorticoids—CRHR1 genotyping, in vitro sensitivity of lymphoid lines)
- McLeod/CREATE Group (in vitro sensitivity, statistical analyses)
- Giacomini & Kroetz/PMT Group (MTX PK, adverse effects in children)
- Julie Johnson/PEAR group (steroid-induced HTN in ALL)
- Crawford/PAT Group (genetics of drug-induced hyperlipidemias)

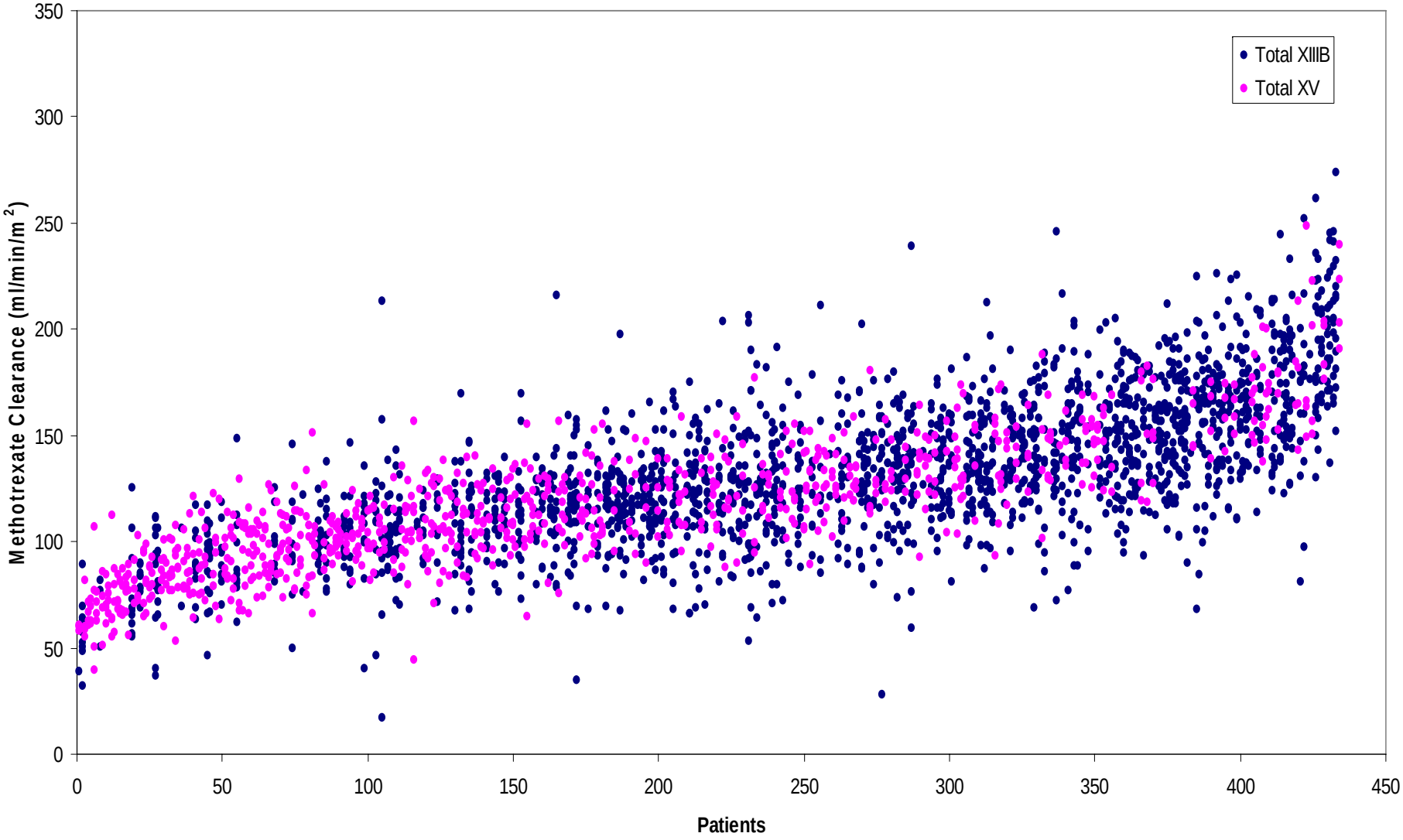
A whole genome approach identifies an organic anion transporter as a major determinant of methotrexate disposition and adverse effects.

Lisa R. Treviño, Noriko Shimasaki, Wenjian Yang, John C. Panetta, Cheng Cheng, Deqing Pei, Diana Chan, Alex Sparreboom, Kathleen M. Giacomini, Ching-Hon Pui, William E. Evans, and Mary V. Relling

Specific Aim

- Use a genome-wide scan to identify germline genetic variation in children with newly diagnosed ALL that is predictive of methotrexate pharmacokinetics and pharmacodynamics

3014 courses of Methotrexate in 434 patients



Principles for studying how genetic variation affects ALL outcome in SJ and COG studies

- **Toxicity and efficacy---in same pts**
- **Treatment-specific**
- **? Race, sex, and subtype-specific**
- **Goal is to ID the polymorphisms**
- **Replication will be needed**
- **Collaborate with other groups**
- **Follow-up with laboratory studies**
- **Minimize redundancy in typing**
- **Create a stable resource of data to be mined**
- **Use all pts (cohorts) rather than case-ctrl design---carry through to relapse and late effects studies**
- **Interface with other biological studies (gene expression, molecular phenotyping of blasts, MRD)**
- **Will continue for at least 10-20 years (maybe forever)**
- **Move testing into therapy as appropriate**

Post-docs/students	Data Analysts/Statisticians	Collaborators
Claudio Rocha	Wenjian Yang	William Evans
Shinji Kishi	Cheng Cheng	Ching-Hon Pui
Jun Yang	Nancy Cox	Kathy Giacomini
Leo Hamilton	Mini Devidas	Stella Davies
Lisa Trevino		Greg Reaman
Chris Hartford	Nancy Kornegay	Michael Borowitz
		Steve Hunger
		Nobuko Hijiya
Deb French	Deqing Pei	Bill Carroll
		Naomi Winick
Alessia Bogni	Wei Liu	Torrey Sandlund
		Julie Johnson
Meyling Cheok	Gary Rosner	Ed Cook
Carmelo Rizzari		Sue Kaste
Terreia Jones		Sima Jeha
Lei Yang		Jeff Rubnitz
Mat Edick		Raul Ribeiro

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Children's Oncology Group

PGRN